IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF TEXAS
SHERMAN DIVISION

AMERICAN CLINICAL LABORATORIES ASSOCIATION, *et al.*, Plaintiffs, v. U.S. FOOD AND DRUG ADMINISTRATION, *et al.*, Defendants.	Case No. 4:24-cv-00479
ASSOCIATION FOR MOLECULAR PATHOLOGY, *et al.* Plaintiffs, v. U.S. FOOD AND DRUG ADMINISTRATION, *et al.*, Defendants.	Case No. 4:24-cv-00824

BRIEF OF DR. RESHMA RAMACHANDRAN, DR. JOSEPH S. ROSS, AND KUSHAL T. KADAKIA AS *AMICI CURIAE* IN SUPPORT OF DEFENDANTS' CROSS-MOTION FOR SUMMARY JUDGMENT AND OPPOSITION TO PLAINTIFFS' MOTIONS FOR SUMMARY JUDGMENT

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IDENTITY AND INTERESTS OF *AMICI CURIAE*

Amici curiae Dr. Reshma Ramachandran, MD, MPP, MHS, Dr. Joseph S. Ross, MD, MHS, and Kushal T. Kadakia, MSc are practicing physicians and leading experts in pharmaceutical and medical device regulatory policy, who have studied and written extensively on the relationship between regulatory standards for drug and medical device approvals and medical product safety and efficacy. *Amici* have been published widely in both top-tier medical and public health journals and national media outlets, platforms which they have used to comment on, and sometimes critique, U.S. Food and Drug Administration (FDA) regulatory policy.

Dr. Ramachandran, Dr. Ross, and Mr. Kadakia are thus well-positioned to explain why FDA's rule on Laboratory Developed Tests (LDTs), 89 Fed. Reg. 37286 (May 6, 2024) (the "LDT Rule") is a reasonable response to seismic changes in the way that LDTs have been manufactured and marketed, which is necessary to protect patients and the public health.

INTRODUCTION

Since 1938, Congress has empowered FDA through the Federal Food, Drug, and Cosmetic Act (FDCA) to protect the public from unsafe and ineffective medical devices, including *in vitro* diagnostic tests (IVDs). *See* 21 U.S.C. § 321(h)(1). Congress clarified this authority in the Medical Device Amendments of 1976 (MDA) and also established a risk-based regulatory framework, one the LDT Rule now applies, which provides that FDA's oversight of a device should be tied to the device's risk to patients. *See* Medical Device Amendments of 1976, Pub. L. 94-295, 90 Stat. 539 (1976); *see also* 89 Fed. Reg. at 37286. Importantly, neither statute contains any suggestion that Congress meant to limit FDA's ability to regulate IVDs based on where a test was made. Nor has FDA ever understood its own authority to be circumscribed in that manner. To the contrary, for

nearly half a century, FDA has asserted its authority to regulate LDTs as medical devices under the FDCA. *See* 89 Fed. Reg. at 37331.

The risk that LDTs would produce inaccurate results that might harm patients was initially relatively low. The tests were "mostly manufactured in small volumes by local laboratories" that used "manual techniques" and "components that were legally marketed for clinical use" to produce LDTs that were similar to well-established diagnostic tests or existing LDTs used to diagnose rare diseases and to meet local patient needs. *See* Framework for Regulatory Oversight of Laboratory Developed Tests, 79 Fed. Reg. 59776, 59777 (Oct. 3, 2014). And the results of these early LDTs "were typically used and interpreted directly by physicians and pathologists working within a single institution that was responsible for the patient." *Id.* Accordingly, and consistent with the risk-based regulatory framework prescribed by the FDCA, FDA did "not enforce[] applicable requirements" for most LDTs, such as registration and listing or pre-market approval of a test's labeling and design. *See* 89 Fed. Reg. at 37286.

However, rapid advancements in laboratory science, especially in genetic sequencing capabilities, brought about "dramatic[]" changes to "the landscape for laboratory testing," which substantially raised the risk profile of LDTs. *See* 79 Fed. Reg. at 59777. LDTs were no longer typified by a laboratory developing a "home brew" test to serve the needs of a patient down the hall, in consultation with the patient's care team. Instead, the emerging and dominant force in this new landscape were "large corporations that nationally market[ed] a limited number of complex, high-risk devices." *Id.* And, without the benefit of FDA oversight, these increasingly complex LDTs also caused real harm: Patients who received false-positive results have been subjected to intense anxiety and unnecessary costs for invasive and risky treatments, while patients with false-

negative results have delayed or foregone necessary care, which has led to worse health outcomes. *See infra* 14-19.[1]

Despite the obvious risk to patient health and safety posed by increasingly ambitious and complex LDTs, FDA has proceeded deliberatively. It has provided industry groups, including Plaintiffs, with many opportunities—over a number of years—to provide substantive input on a regulatory approach that would minimize disruption to industry innovation, the benefits of which FDA has consistently acknowledged, while taking proactive steps to protect patients. The LDT Rule strikes that balance but should not be understood as attempting something novel. Rather, although LDTs will soon be required to comply with FDCA requirements for medical devices, the LDT Rule as a whole merely continues FDA's longstanding, congressionally authorized approach of calibrating regulatory requirements to a medical device's risk profile.

Because FDA has clear authority and ample justification for the LDT Rule, the Court should grant Defendants' motion for summary judgment.

ARGUMENT

Amici set forth two arguments below. Section I describes the relevant regulatory history, which shows that the LDT Rule is a continuation of FDA's longstanding approach to regulating LDTs and does not raise "major questions." Section II explains how the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and the FDCA serve distinct, albeit complementary, regulatory purposes, a point further illustrated by examples of LDTs manufactured in CLIA-compliant laboratories that nevertheless caused real harm to patients and the public health.

[1] *See also* Off. of Pub. Health Strategy & Analysis, FDA, *The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies* 2 (Nov. 16, 2015), https://tinyurl.com/2a9m7xnw [hereinafter "Case Studies"].

I. The FDA has consistently asserted its authority over time, which shows that the LDT Rule is neither an unheralded nor transformative departure from prior practice.

Plaintiffs assert that the LDT Rule, among its other supposed infirmities, raises "major questions" because it allegedly represents a "transformative expansion" of FDA's authority, which has been newly "discover[ed] in a long-extant statute." *See* ACLA Summ. J. Br. at 33, ECF No. 20 (quoting *West Virginia v. EPA*, 597 U.S. 697, 724 (2022)); *see also* AMP Summ. J. Br. at 25-26, ECF No. 27. These arguments are undercut, however, by a complete accounting of the regulatory history, which shows that, "[o]ver 30 years ago, FDA unambiguously stated that it has authority over [LDTs]" but, consistent with the FDCA's prescribed risk-based approach for regulating devices and the enforcement discretion granted to FDA by Congress, FDA has generally exercised a policy of non-enforcement against LDTs. *See* 89 Fed. Reg. at 37352; *see also* FDA Summ. J. Br. at 6-9, ECF No. 54. More than a decade ago—in response to substantial changes to how LDTs were manufactured and used, as well as actual evidence of patient harm and clinician confusion—FDA began exploring changes to its general non-enforcement policy. *See* 89 Fed. Reg. at 37352. It has done so deliberately and with consistent, robust opportunities for stakeholders, including Plaintiffs, to provide input. *Id.* at 37361. More recently, FDA "has applied [its FDCA device] authority to hundreds of laboratory-made IVDs, including LDTs, without legal challenge." *Id.* at 37352. Viewed in that light, it is apparent that the LDT Rule hardly reflects the kind of extraordinary assertion of newly discovered authority that courts have found to raise "major questions."

Congress initially authorized the federal regulation of medical "devices" in 1938 through passage of the FDCA. At the time, "device" was defined to encompass "instruments, apparatus, and contrivances, including their components, parts, and accessories, intended (1) for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; or (2) to

affect the structure or any function of the body of man or other animals." Food, Drug, & Cosmetic Act, ch. 675, 52 Stat. 1040, 1041 (1938). That definition was read narrowly, however, and understood to encompass only "the types of items Congress suggested in the debates, such as electric belts, quack diagnostic scales, and therapeutic lamps, as well as bathroom weight scales, shoulder braces, air conditioning units, and crutches." *United States v. Bacto-Unidisk*, 394 U.S. 784, 799-800 (1969). Accordingly, FDA frequently resorted to its comparatively broader authority to regulate "drugs," *see, e.g.*, *id.*, although it also maintained "that as a matter of law" it had authority to regulate *in vitro* diagnostic products, *see* Labeling Requirements and Procedures for Development of Standards for In Vitro Diagnostic Products for Human Use, 38 Fed. Reg. 7096, 7096 (Mar. 15, 1973).[2]

Advances in science and technology led to the development of increasingly complicated medical devices, however, which also revealed the inadequacy of this authority to protect consumers. In response, Congress passed the MDA, which amended the FDCA by "creat[ing] a comprehensive system for the regulation of devices intended for human use," 89 Fed. Reg. at 37286. *See* Pub. L. 94-295, 90 Stat. 539 (1976). Among other things, the MDA expanded the FDCA's definition of "device" to include:

> an instrument, apparatus, *implement, machine,* contrivance, *implant, in vitro reagent, or other similar or related article*, including any component, part, or accessory, which is . . . . intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals[.]

21 U.S.C. § 321(h)(1) (amended language in italics). This amendment reflected Congress' intention for FDA to regulate emerging forms of medical devices, including "in vitro reagents,"

[2] FDA's statement was made in a final rule that "announc[ed] regulatory requirements for IVD products, including systems," and "contained no carveout or exception for laboratories." *See* 89 Fed. Reg. at 37328.

without regard for where or by whom they are manufactured. *See* 89 Fed. Reg. at 37286.[3] The MDA further established a framework through which FDA would apply "various levels of oversight for medical devices, depending on the risks they present." *Riegel v. Medtronic, Inc.*, 552 U.S. 312, 316-17 (2008).[4]

Consistent with the MDA's risk-based regulatory scheme, FDA initially "focused primarily on regulation of commercially distributed tests from diagnostic manufacturers"[5]—a decision justified by the potentially broad reach of these tests—though it did nothing to disclaim its authority to regulate LDTs. To the contrary, in a 1977 rulemaking, FDA clarified that clinical laboratories "whose primary responsibility to the ultimate consumer is to dispense or provide a service through the use of a previously manufactured device" were exempt from FDCA registration requirements. Establishment Registration and Premarket Notification Procedures, 42 Fed. Reg. 42520, 42528 (Aug. 23, 1977). FDA's decision to include that exemption thus provided clinical laboratories with fair notice that it understood their products to be subject to the FDCA's

[3] Broadly speaking, an "in vitro reagent" refers to a piece of medical technology, including an in vitro diagnostic device (IVD), that uses samples taken from the human body—e.g., blood or tissue—to diagnose diseases.

[4] Under this regime, "Class I" devices are "subject to the lowest level of oversight: "general controls," such as labeling requirements"; "Class II" devices are "subject in addition to 'special controls' such as performance standards and postmarket surveillance measures"; and "Class III" devices are those which cannot be made reasonably safe and effective with less oversight and are used for "supporting or sustaining human life" or "preventing impairment of human health" or which "presents a potential unreasonable risk of illness or injury." *Riegel*, 552 U.S. at 316-17 (citing 21 U.S.C. §§ 360c(a)(1)(A)–(C)).

[5] *See* Jonathan R. Genzen et al., *Laboratory-Developed Tests: A Legislative and Regulatory Review*, 63 Clinical Chemistry 1575, 1577 (2017), https://tinyurl.com/3zw7mk94; *see also* Amanda K. Sarata, Cong. Rsch. Serv., IF12628, *Regulation of Laboratory-Developed Tests: FDA's Proposed Rule*, at 1 (Apr. 8, 2024), https://tinyurl.com/2s4ytkxt ("In general, FDA has maintained that it has clear regulatory authority over LDTs, as it does with all IVDs that meet the definition of device in the [FDCA].").

device regulations because the exemption would have made no sense otherwise. *See* 89 Fed. Reg. at 37328.

Within a decade, further advances in science—especially the development of the polymerase chain reaction (PCR)[6] in 1985—caused an explosion of IVDs of increasing technical complexity,[7] including for infectious diseases like HIV, hepatitis, and influenza.[8] These new tools promised earlier detection of serious diseases through less invasive means, but greater reliance on these novel tests—unregulated in the case of LDTs—also carried substantial risk for patients.[9]

In response to these advances, FDA promulgated additional LDT policies.[10] First, in 1992, FDA published a draft guidance document, which stated that devices made "from products already on the market, or from components, and utilizing these unapproved products for diagnostic purposes"—i.e., LDTs—were "subject to the same regulatory requirements as any unapproved medical device[.]"[11] FDA never issued a final version of this guidance but, in response to a petition submitted by "a law firm that represents clinical laboratories," which requested that any final guidance exclude LDTs,[12] FDA once again stated that it had authority to regulate tests "developed

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[6] PCR "is a fast and inexpensive technique used to . . . copy . . . small segments of DNA." Nat'l Hum. Genome Rsch. Inst., *Polymerase Chain Reaction (PCR) Fact Sheet* (Aug. 17, 2020), https://tinyurl.com/mrynk68m.

[7] Genzen et al., *supra* note 5, at 1578.

[8] *See* Hanliang Zhu et al., *PCR Past, Present and Future*, 69 BioTechniques 317, 317 (2020), https://tinyurl.com/bdzjey4h.

[9] *See Deadly Mistakes: Are Laboratory Results Reliable?: Hearings Before the Subcomm. on Regul. & Bus. Opportunities of the House Comm. on Small Bus.*, 100th Cong., Serial No. 100-43 (1988) (highlighting regulatory gaps affecting patient safety and public health).

[10] *See* Genzen et al., *supra* note 5, at 1578.

[11] *See* FDA, *Commercialization of Unapproved In Vitro Diagnostic Devices Labeled for Research and Investigation*, at 4 (Aug. 3, 1992), https://tinyurl.com/4wamup5c.

[12] *See* Citizen Petition of Hyman, Phels & McNamara, P.C. to FDA, at 2 (Oct. 22, 1992), https://tinyurl.com/4tszxhwv.

by clinical reference laboratories strictly for in-house use as medical devices."[13]

Next, in a 1997 final rule regulating the components from which LDTs are constructed, FDA stated that "clinical laboratories that develop [LDTs] are acting as manufacturers of medical devices and are subject to FDA jurisdiction under the [FDCA]."[14] Finally, in draft guidance released in 2007, FDA reiterated that it had authority under the FDCA to regulate "'clinical laboratories that develop (in-house) tests'" as medical devices. Draft Guidance for Industry and Food and Drug Administration Staff; In Vitro Diagnostic Multivariate Index Assays, 72 Fed. Reg. 41081, 41081-82 (July 26, 2007). FDA also announced that it would begin enforcing premarket controls over LDTs using non-standard ingredients, while continuing to "generally exercise[] enforcement discretion" over low-risk LDTs. *Id.* at 41082.

Between 2010 and 2014, FDA took further steps to clarify and refine its risk-based approach to regulating LDTs, including through stakeholder meetings, while also continuing to emphasize its authority to regulate LDTs under the FDCA. *See* Oversight of Laboratory Developed Tests, 75 Fed. Reg. 34463, 34463 (June 17, 2010). For instance, at a public meeting in 2010, FDA reminded the gathered stakeholders that the FDCA's pre-market review requirements "actually already appl[ied]" to LDTs because they came directly from the FDCA; FDA had "simply, as a matter of policy, determined not to exercise or not to enforce that authority *as of right now*."[15]

By 2014, FDA had developed draft guidance, which laid out a "risk-based framework for addressing the regulatory oversight of [LDTs]," and "describe[d] FDA's priorities for enforcing

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[13] *See* Letter from D. Bruce Burlington, M.D., Director, Center for Devices and Radiological Health, to Hyman, Phelps & McNamara, P.C., at 1 (Aug. 12, 1998), https://tinyurl.com/3awapkee.

[14] Genzen et al., *supra* note 5, at 1579 (quoting Medical Devices; Classification/Reclassification; Restricted Devices; Analyte Specific Reagents, 62 Fed. Reg. 62243, 62249 (Nov. 21, 1997)).

[15] *See* FDA Public Meeting on Oversight of Laboratory Developed Tests, Transcript at 82:11-19 (J. Shuren) (July 19, 2010), https://tinyurl.com/5erbf389 (emphasis added) [hereinafter "FDA July 19, 2010 Mtg. Tr."]; Genzen et al., *supra* note 5, at 1581.

pre- and post-market requirements for LDTs, and the process by which FDA intend[ed] to phase in enforcement of FDA regulatory requirements for LDTs over time." *See* 79 Fed. Reg. at 59776. FDA explained that a more proactive approach was necessary in light of the "dramatic[]" changes it had observed to "the landscape for laboratory testing in general, and LDTs along with it." *Id.* at 59777. FDA summarized these changes, as follows:

> In 1976, LDTs were mostly manufactured in small volumes by local laboratories. Many laboratories manufactured LDTs that were similar to well-characterized, standard diagnostic devices, as well as other LDTs that were intended for use in diagnosing rare diseases or for other uses to meet the needs of a local patient population. LDTs at the time tended to rely on the manual techniques used by laboratory personnel. LDTs were typically used and interpreted directly by physicians and pathologists working within a single institution that was responsible for the patient. In addition, historically, LDTs were manufactured using components that were legally marketed for clinical use (i.e., general purpose reagents, immunohistochemical stains, and other components marketed in compliance with FDA regulatory requirements).

79 Fed. Reg. at 59777; *see also* 75 Fed. Reg. at 34464 (stating that it was "time to reconsider [FDA's] policy of enforcement discretion over LDTs").

FDA contrasted that with the current landscape, where LDTs were frequently made and performed by laboratories with no direct relationship to patients or their providers, despite the fact that many LDTs were promising to provide results that would use a patient's genetic makeup to precisely guide their treatment. *See* 79 Fed. Reg. at 59777. Moreover, LDTs were increasingly being "manufactured with components and instruments that [were] not" separately approved by FDA for clinical use, and many were also relying on "complex, high-tech instrumentation and software to generate results and clinical interpretations." *See id.* FDA also noted how changes to the business model for laboratories selling LDTs had changed substantially since 1976. Specifically, online advertising, as well as the availability of "overnight shipping and electronic delivery of [test results]," had made it extremely profitable for LDT manufacturers to market their

devices "nationally and internationally." *See id.*[16] Ultimately, the LDT manufacturers defining this new landscape were "large corporations that nationally market[ed] a limited number of complex, high-risk devices" to a large number of dispersed patients, *see* 79 Fed. Reg. at 59777, sometimes doing so directly and bypassing healthcare providers entirely.[17]

Assessing these changes, FDA reasonably concluded that "a significant shift" had occurred "in the types of LDTs developed, the business model for developing them, and the potential risks they pose to patients," which made its longstanding "policy of general enforcement discretion toward LDTs . . . *no longer appropriate*." *See* 79 Fed. Reg. at 59777 (emphasis added). Despite this awareness, FDA continued to deliberate and engage with industry groups, as well as Congress, in order to find a satisfactory path forward. When legislative efforts stalled, and with the addition of "[o]ther evidence, including published literature and the FDA's experience with tests to diagnose COVID-19," all of which "suggest[ed] that the situation [wa]s getting worse," FDA was compelled to act.[18]

* * *

What this regulatory history shows is that FDA has been consistent in its understanding and explanation of its own authority for half a century, while also gradually refining its approach

[16] *See also* Thomas M. Burton, *Is Lab Testing the 'Wild West' of Medicine?*, Wall Street Journal (Dec. 10, 2015) (describing the daily "onslaught of about 30,000 specimens" of "human blood and cell samples," which are delivered via FedEx each morning "to more than 40 laboratories at the . . . Mayo Clinic" where they are tested for answers to "life-or-death questions: Does the patient have cancer? Which drug treatment has the best chance of success?"). The Mayo Clinic Laboratories is a member of Plaintiff ACLA. *See* Am. Clinical Laboratories Assn., *Members*, https://tinyurl.com/5n6stkzb (last accessed Oct. 31, 2024).

[17] *See also* Liz Richardson et al., The Pew Charitable Trusts, *The Role of Lab-Developed Tests in the In Vitro Diagnostics Market*, at 2 (2021), https://tinyurl.com/557jxxna (describing the "many direct-to-consumer genetic tests that claim to determine an individual's risk of developing cancer and other diseases," most of which "are unapproved LDTs").

[18] *See* FDA, Press Release, *FDA and CMS: Americans Deserve Accurate and Reliable Diagnostic Tests, Wherever They Are Made* (Jan. 18, 2024), https://tinyurl.com/4y8cu9cn.

to exercising that authority, in response to new facts and circumstances. That shows reasoned agency decision-making, not an extraordinary power grab that might raise "major questions."

II. The LDT Rule reasonably responds to evidence that LDTs have injured patients and the public health in a manner best addressed by FDA oversight under the FDCA.

Plaintiffs further claim that FDA lacks authority to regulate LDTs because Congress tasked the Centers for Medicare & Medicaid Services (CMS) with regulating clinical laboratories through the Clinical Laboratory Improvement Amendments of 1988 (CLIA), Pub. L. 100-578 (Oct. 31, 1988), which would render regulation under the FDCA duplicative and unnecessary. *See, e.g.*, AMP Summ. J. Br. at 28-32; *see also* ACLA Summ. J. Br. at 30. But that argument overlooks the distinct, albeit complementary, regulatory purposes served by CLIA and the FDCA. Plaintiffs also overlook, or cursorily dismiss, evidence showing that, in the absence of FDA oversight, inaccurate and unreliable LDTs have entered the market and harmed patients and the public health.

A. CLIA's requirements are insufficient to ensure that LDTs produce reliable and accurate results.

As FDA has explained at length, both CLIA and the FDCA play an important role in ensuring the accuracy and reliability of LDTs. *See* 89 Fed. Reg. at 37313; *see also* FDA Summ. J. Br. at 36-41. Their separate functions, however, make it abundantly clear that CLIA "is not a substitute for FDA oversight," as both FDA and CMS have long acknowledged. *See* 89 Fed. Reg. at 37292.[19]

Fundamentally, CLIA is concerned with ensuring that laboratories and laboratory employees are functioning consistently well, such that the laboratory environment does not

[19] *See also* FDA July 19, 2010 Mtg. Tr., *supra* note 15, at 84:6-11(A. Gutierrez) (FDA official describing CLIA's lack of "clinical validity" oversight as "[p]robably the biggest [regulatory] gap of all"); CMS, *Laboratory Developed Tests (LDTs): Frequently Asked Questions* 3 (Oct. 22, 2013), https://tinyurl.com/yc28n4e9 [hereinafter "CMS FAQ"].

interfere with the production of accurate and reliable test results. *See* 42 U.S.C. § 263a(a), (c). Accordingly, CMS' implementing regulations "include requirements pertaining to proficiency testing, laboratory personnel qualifications, test ordering and reporting, quality control, and the development and use of laboratory processes and procedures." 89 Fed. Reg. at 37313-14.

Importantly, if LDTs are regulated under CLIA alone, many of the risks to patient and public safety posed by the current LDT landscape, *see supra* at 14-19, will be out of reach of federal oversight. For instance, CLIA does not enable CMS to prevent flawed LDTs from reaching market; CLIA does not grant CMS premarket review authority, and it mandates that laboratory inspections will occur biennially. *See* 42 U.S.C. § 263a(g)(2). Nor does CLIA enable CMS to scrutinize LDT results to ensure they are *clinically* valid—i.e., that they accurately "identif[y], measure[], or predict[] the presence or absence of a clinical condition or predisposition in a patient."[20] CMS' task under CLIA is instead to ensure that a laboratory can produce *analytically* valid results "in the laboratory's own environment"—i.e., that environmental factors within a laboratory do not prevent it from performing tests that accurately identify the substances the tests are supposed detect.[21]

CLIA is also ill-suited to protect patients from LDTs, or other kinds of devices that incorporate intangible elements, that produce inaccurate or unreliable results because of faulty software, biased algorithms, unaddressed cybersecurity vulnerabilities, and the like.[22] *See* 89 Fed.

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[20] *See id.*

[21] *See* CMS FAQ, *supra* note 19, at 3 (citing 42 C.F.R. § 493.1253(b)(2)).

[22] *Amici* agree with FDA that LDTs "are physical products made from physical items" and that, accordingly, the Court does not need to decide whether FDA may regulate only "tangible, physical products" as "devices," as Plaintiffs argue. *See* FDA Summ. J. Br. at 26. Furthermore, adopting Plaintiffs' narrow reading of the FDCA could impede FDA's ability "to regulate devices that do not have a tangible form (such as software)," *see id.*, and, in turn, seriously undermine FDA's ability to ensure that the public is not harmed by novel and high-risk medical devices. The full

Reg. at 37289 (noting cybersecurity risks some LDTs face). For instance, medical devices that incorporate artificial intelligence (AI) are already used to analyze radiology imaging, "process and analyze data from wearable sensors to detect diseases or infer the onset of other health conditions," and "predict patient outcomes based on data collected from electronic health records, such as determining which patients may be at higher risk for disease or estimating who should receive increased monitoring."[23] These tools "offer[] unique opportunities to improve health care and patient outcomes," but have also "resulted in inaccurate, even potentially harmful, recommendations for treatment," errors that are attributable to "bias in the information used to build or train the AI, inappropriate weight given to certain data points analyzed by the tool, and other flaws."[24] CLIA, however, is not well-suited to protect patients from these kinds of issues, as even industry groups acknowledge. *See, e.g.*, Br. of the Assn. for Academic Pathology at 18, ECF No. 51 (acknowledging that, under existing law, CLIA is not well-suited "to address the use of AI in diagnostic testing").

By contrast, FDA and the risk-based regulatory authority it exercises under the FDCA is well-suited to respond to the concerns enumerated above and ensure that LDTs produce clinically valid results that are supported by methodologically sound studies, transparently labeled, and accurately marketed to patients and providers.

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sweep of the risk to the public that might result if the Court adopts Plaintiffs' "tangible device" limitation is hardly clear from the record before the Court, which should counsel extreme caution, if the Court does reach that argument.

[23] *See* The Pew Charitable Trusts, *How FDA Regulates Artificial Intelligence in Medical Products*, at 2 (July 2021), https://tinyurl.com/5n7myv42.

[24] *Id.* at 1.

B. Without FDA oversight, LDTs have produced inaccurate and unreliable results, which have exposed patients to substantial risk and concrete harm.

As the structural differences between CLIA and the FDCA show, prohibiting FDA from regulating LDTs, as Plaintiffs aim to do, will leave a yawning regulatory gap through which unreliable and inaccurate LDTs will enter the marketplace. Those flawed tests will place patients at risk and frustrate their ability to make informed healthcare decisions. These concerns are not speculative. LDTs offered by CLIA-compliant laboratories have, in a range of cases, produced inaccurate and unreliable results, which exposed patients to unnecessary risk including, in extreme cases, death. *See* Case Studies at 8-18 (discussing LDTs that produced false-positive results, false-negative results, or both); *see also* Angela M. Calienda & Kimberly E. Hanson, *Point-Counterpoint: The FDA Has a Role in Regulation of Laboratory-Developed Tests*, 54 J. Clinical Microbiology 829, 829 (2016), https://tinyurl.com/4f2be9zr (estimating that inaccurate LDTs likely contribute to the 10 percent of patient deaths attributable to "[d]iagnostic errors").

The case studies discussed below highlight harm that LDTs have caused and the difference that FDA oversight might have made.

1. OvaSure.

OvaSure is an LDT that analyzes blood samples to identify certain biomarkers that were believed to have an association with ovarian cancer, "one of the more common and deadly cancers" in the United States and a disease for which early detection is essential. *See* Case Studies at 9-11. OvaSure was first marketed in 2008 and was billed as an exceptionally precise screening test "for early-stage ovarian cancer in high-risk women," a claim based on a validation study that enrolled a population with a cancer rate far higher than the general population's, which resulted in OvaSure's grossly inflated expectations for its accuracy. *See id.* at 11. In reality, OvaSure would have returned false-positive results approximately 93 percent of the time. *See id.* (estimating that,

if "the actual population prevalence of 0.04% was used, . . . only 1 in 15 patients who tested positive actually had the disease").

As a consequence of OvaSure's misleading marketing and inaccurate test results, patients who received a false-positive result indicating a cancer diagnosis unnecessarily experienced anxiety and fear. Some likely also spent additional time and money on further diagnostic testing. Worst of all, patients who trusted their false-positive diagnosis might have undertaken aggressive treatments, including "surgery to remove the ovaries, the uterus, and any visible cancer, followed by chemotherapy and sometimes radiation." *See id.* at 10-11. These risks might have been avoided had OvaSure been subjected to FDA oversight, which would have scrutinized its validation study population, as well as its marketing claims.

2. Non-invasive prenatal screening tests (NIPTs).

Non-invasive prenatal screening tests (NIPT) are offered to pregnant patients who have either "test[ed] positive on an initial non-invasive test or are otherwise at high risk" for a pregnancy involving "[a] fetus with an extra chromosome," a condition called "trisomy." *See id.* at 17.[25] NIPTs screen for chromosomal abnormalities by analyzing maternal blood samples, which is a far safer, cheaper, and less invasive way to screen for indications of trisomy than available alternatives. *Id.* Numerous companies in the United States market NIPTs and promising "very high accuracy rates." *See id.*

The marketing of NIPTs was effective but misleading: "Hundreds of thousands of pregnant women . . . used these noninvasive prenatal tests" in the first few years of their availability,

[25] The most common type of trisomy is trisomy 21 (Down syndrome)." *See* Cleveland Clinic, *Trisomy* (May 3, 2022), https://tinyurl.com/2xev6dm4. Many children with Down Syndrome lead healthy and "relatively independent lives" but, tragically, other types of trisomy often cause miscarriages or, for children who are carried to term, "significant birth defects" and premature death, often "within a year of birth." *See* Case Studies at 17.

believing there was "little reason to doubt their effectiveness."[26] Trisomy is an incredibly rare condition, however, so NIPT manufacturers should have understood—and warned consumers—that "more false-positive than true-positive results" were to be expected. *See* Case Studies at 17. In practice, positive results from NIPTs were "wrong 50 percent or more of the time,"[27] which should have prompted patients who received positive NIPT results to pursue "follow-up testing for confirmation." Case Studies at 17.[28] Those who sought additional confirmation could still be harmed, however, because the additional testing necessary to confirm trisomy is invasive and potentially risky for the pregnancy. Case Studies at 17. Unfortunately, because of how the tests were marketed, many women understood their NIPT *screening* results to be definitive *diagnostic* results and made irreversible decisions without the benefit of a more accurate diagnostic test.[29]

Although clinicians may be able to identify suspect test results, see through marketing bluster, and understand a test's limitations, many do not and place their trust in test results they assume are clinically valid and accurate. *See, e.g.*, 89 Fed. Reg. at 37313 (noting the many

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[26] *Prenatal Tests Have High Failure Rate, Triggering Abortions*, NBC News (Dec. 14, 2014), https://tinyurl.com/4hvdbrmt.

[27] *See Prenatal Tests Have High Failure Rate*, *supra* note 26.

[28] *See* FDA, *Genetic Non-Invasive Prenatal Screening Tests May Have False Results: FDA Safety Communication* (Apr. 19, 2022), https://tinyurl.com/5yz7ms23 (warning providers "of the risks and limitations of using these screening tests" and cautioning against using "the results from these tests alone to diagnose chromosomal (genetic) abnormalities or disorders"); *see also* American College of Obstetricians and Gynecologists, *NIPT Summary of Recommendations* (accessed on Oct. 28, 2024), https://tinyurl.com/2m8htnc4 (advising that "[p]atients with a positive screening test result . . . undergo genetic counseling and a comprehensive ultrasound evaluation with an opportunity for diagnostic testing to confirm results.").

[29] *See Prenatal Tests Have High Failure Rate*, *supra* note 26 (describing study finding "that 22 (6%) of women who received positive results obtained abortions without a follow-up invasive diagnostic test"); *see also* Miriam Kupperman et al., *Effect of Enhanced Information, Values Clarification, and Removal of Financial Barriers on Use of Prenatal Genetic Testing*, 313 JAMA 200, 200 (2015), https://tinyurl.com/pfcmwsn9 (noting "[l]ow uptake rates of invasive testing among women who receive positive screening results . . . particularly among women of lower literacy and numeracy levels").

clinicians "who do not understand the limitations of tests and do not consider that a test result provided by a test may be incorrect"); *see also* Calienda and Hanson, *Point-Counterpoint*, at 829.

The addition of FDA premarket review, including the imposition of labeling requirements, would have narrowed this knowledge gap by making "transparent information regarding [test] performance" and limitations more accessible to patients and providers. *See* 89 Fed. Reg. at 37324. Without that information, which CLIA does not require and NIPTs manufacturers declined to provide, many expecting patients unwittingly made uninformed choices about their healthcare.

3. Statincheck.

"Statincheck" is an LDT that detects a specific genetic mutation, the presence of which was believed to indicate that a patient had coronary artery disease (CAD) and would likely benefit from treatment with a class of cholesterol medication called "statins."[30] Between 2008 and 2010, Statincheck's manufacturer successfully marketed the genetic test to cardiologists and primary care physicians, offering a quick means of identifying CAD and a suitable course of treatment.[31] As a result of its successful marketing, Statincheck's manufacturer sold more than 160,000 tests, which cost roughly $100 each.[32] Statincheck's success was short lived, however, because high-quality studies demonstrated that there was likely no "significant correlation" between the genetic mutation Statincheck identified and CAD.[33]

The risk to patients introduced by Statincheck's clinically irrelevant results were severalfold. Those who received false-positive results could have been prescribed a statin

[30] *See* Eric J. Topol & Samir B. Damani, *The KIF6 Collapse*, 56 J. Am. College Cardiology 1564, 1564 (2010), https://tinyurl.com/yhhdka7p; *see also* Mayo Clinic, *Statins: Are These Cholesterol-Lowering Drugs Right For You?* (Mar. 6, 2024), https://tinyurl.com/yrxf9mct.

[31] Topol and Damani, *supra* note 30, at 1564.

[32] *Id.*

[33] *Id.*

unnecessarily and possibly suffered side effects "rang[ing] from muscle pain and cramping to more serious reactions such as nerve damage, mood, sleep and cognitive impairment, and, rarely, muscle breakdown leading to kidney failure." *See* Case Studies at 19-20. Or, in the case of a false-negative result, Statincheck patients might have been deprived of a chance to "prevent[] cardiovascular events and deaths." *See id.* In either case, the widespread introduction of a test that lacked clinical validity compromised clinician and patient decision-making.

For several reasons, these harms likely would have been prevented had Statincheck been subjected to FDA oversight. Most glaringly, Statincheck likely would not have reached the market had the LDT Rule been in effect because FDA's premarket review would have uncovered its reliance on "antiquated . . . methodologies" that were "well-known to be plagued by false-positive results" to show clinical validity.[34] The LDT Rule would also close a loophole that Statincheck's manufacturer exploited. After seeking FDA approval, Statincheck's manufacturer withdrew its application because FDA found "the evidence submitted was insufficient to support the test's safety and effectiveness." *See* Case Studies at 20. Instead, Statincheck's manufacturer simply began marketing the test as an LDT; it "remains on the market as an LDT" today and its manufacturer continues to make erroneous claims about Statincheck's clinical validity. *Id.*

4. Genetic testing for hypertrophic cardiomyopathy.

"Hypertrophic cardiomyopathy (HCM) is a disease in which the heart muscle becomes thickened," which "can make it harder for the heart to pump blood."[35] A "leading genetic-testing laboratory" believed that it had identified a genetic marker that indicated HCM and, on that basis,

[34] *Id.*

[35] Mayo Clinic, *Hypertrophic Cardiomyopathy* (Feb. 23, 2024), https://tinyurl.com/yh78u9e6.

began marketing an LDT that could determine if the marker was present in patients.[36] The laboratory failed to appreciate that the genetic variations it interpreted as confirming HCM "were significantly more common among [B]lack Americans than among white Americans," however, which resulted in "[m]ultiple patients, all of whom were of African or unspecified ancestry," being misclassified as having genetic markers of HCM. *See id*.

Erroneously telling a patient they have genetic markers of HCM "can have far-reaching adverse consequences within the family." *See id.* at 656. Most acutely, a patient who has clinical evidence of HCM, but lacks a definitive diagnosis, "such as young athletes with modest [symptoms] and a family history of sudden cardiac death," might overestimate the need for invasive surgery. *Id.* Because HCM is hereditary, relatives of the misclassified patient might also be needlessly subjected to "prolonged at-risk screening," advised to stop playing sports or enjoying other recreational activities, or simply suffer unnecessary "stress and economic burden." *Id.* Conversely, relatives of a patient who is incorrectly told they lack genetic markers for HCM "are given false reassurance that further surveillance is unnecessary," which deprives them of an opportunity to take appropriate preventative action. *Id.* Diagnosis errors, if caught and disclosed, may also "engender[] confusion and distrust" between patient and provider. *See id.*

The methodological flaw that produced the HCM misclassifications might have been avoided if the LDT had been subjected to FDA premarket review. Specifically, the composition of the validation study population would have been carefully reviewed and any resulting limitations in the test's clinical utility would have been disclosed to patients and providers. *See* 89 Fed. Reg. at 37326.

[36] *See* Arjun K. Manrai et al., *Genetic Misdiagnoses and the Potential for Health Disparities*, 375 New England J. Med. 655, 655 (Aug. 18, 2016), https://tinyurl.com/4z4mkeab.

CONCLUSION

For the foregoing reasons, the Court should deny Plaintiffs' motions for summary judgment and grant Defendants' motion for summary judgment.

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Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on November 4, 2024, a true and accurate copy of the foregoing document was filed electronically via CM/ECF and served on all counsel of record.

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Date: November 4, 2024